(FILE 'HOME' ENTERED AT 14:55:30 ON 13 JUL 2000)

FILE 'CAPLUS' ENTERED AT 14:55:43 ON 13 JUL 2000

L1 1567 S RACEMIZ?(L)(AMINO(W)ACID?)
L2 144 S L1 AND (PROLIN? OR HOMOPROLIN?)
L3 2 S L2 AND PIPERIDIN?

AN 1967:473852 CAPLUS
DN 67:73852
TI Studies on optically active **amino acids**. XII. Synthesis, resolution and **racemization** of bicyclic .alpha.-amino ketones
AU Kunieda, Takehisa; Koga, Kenji; Yamada, Shunichi
CS Univ. Tokyo, Tokyo, Japan
SO Chem. Pharm. Bull. (1967), 15(3), 337-44
CODEN: CPBTAL
DT Journal
LA English
GI For diagram(s), see printed CA Issue.
AB cf. CA 67: 54417t. A mixt. of 32 g. L-**proline** Et ester (I) [[.alpha.]8D -43.5.degree. (c. 3.8, all in EtOH)] and 50 ml. freshly distd. CH2:CHCO2Et was refluxed 6.3 hrs. in 40 ml. EtOH, low boiling fractions were removed in vacuo, and the residue was distd. to yield 47.2 g. Et (-)-2-(ethoxycarbonyl)-1-pyrrolidinepropionate (II), b2 113-20.degree.; [.alpha.]15D -66.4.degree. (c 1.7). II (47.2 g.) in 150 ml. abs. PhMe was added to a suspension of alc. free NaOH (from 4.7 g. Na) in 100 ml. abs. PhMe. The mixt. was refluxed 1.5 hrs. with stirring under N, cooled, extd. with .apprx.200 ml. H2O. The aq. ext. was treated with 230 ml. concd. HCl, the mixt. heated 1.7 hrs. on a water bath until the FeCl3 test was neg. The mixt. was made strongly basic with K2CO3, extd. with ether, and the ext. dried and distd. to yield 9.5 g. hexahydro-1H-pyrrolizin-1-one (III), b4 65.degree.; [.alpha.]9D -49.7.degree. (c 2.5) (unstable in air); [.alpha.]9D -59.2.degree. (c 2.3, dioxane) [picrate m. 165-7.degree. (EtOH); oxime HCl salt, m. 172-3.degree. (EtOH), [.alpha.]25D .+-. 0.degree. (c 1); oxime m. 158-60.degree.]. L-Pipecolic acid Et ester (3.5 g.) and 20 ml. freshly distd. CH2:CHCO2Et in 20 ml. EtOH was refluxed 5.5 hrs. to yield 3.4 g. Et (-)-2-(ethoxycarbonyl)-1-**piperidinepropionate** (IV), b0.5 127-32.degree.; [.alpha.]27D -26.7.degree. (c 2.1). IV (3.4 g.) on treating with NaOEt (as for III) yielded 42% hexahydro-1(5H)-indolizinone (V), b1-2 65-70.degree.; [.alpha.]25D .+-.0.degree. (c 5.8) (unstable liquid) [oxime m. 115-16.degree. (iso-PrOH-iso-Pr2O); picrate m. 170-1.degree. (Me2CO); picrolonate m. 174-5.degree. (EtOH)]. dl-V (5 g.) and 11.5 g. d-3-bromo-8-camphorsulfonic acid (Va) in 20 ml. Me2CO was kept overnight in a refrigerator to yield 3.2 g. (-)-hexahydro-1(5H)-indolizinone 3-bromo-8-camphorsulfonate, m. 160-1.5.degree. (Me2CO); [.alpha.]15D 38.7.degree. (c 1.25, H2O). The salt (2 g.) in 5 ml. H2O was made strongly basic with K2CO3 and extd. with C6H6 to yield 0.46 g. (-)-V, b1-2 68-70.degree.; [.alpha.]24D -105.degree. (c 4.6); [.alpha.]24D -107.3.degree. (c 0.8, dioxane) [oxime HCl salt m. 193-4.degree. (EtOH-iso-Pr2O) [.alpha.]24D -22.0.degree. (c 1, H2O)]. The enantiomeric base V, b5 80.degree.; [.alpha.]20D 30.degree. (c 1.28) was also obtained on similar treatment of the mother liquor. IV (7.5 g.) was added to a suspension of NaOEt (from 0.7 g. Na) in 80 ml. abs. PhMe, the mixt. refluxed 2.5 hrs. under N, cooled and extd. with 40 ml. H2O. The aq. ext.

was neutralized by adding Dry Ice or HOAc, extd. with ether and CH2Cl2, and the combined ext. evapd. in vacuo to yield 1.5 g. Et octahydro-1-oxo-2-indolizine-carboxylate (VI), b0.6 105-7.degree.; [.alpha.]27D .+-. 0.degree. (c 3.8). A soln. of 19 g. II and 30 g. Et 4-bromobutyrate in 60 ml. Me2CO was stirred 3.5 hrs. under N in the presence of 20 g. anhyd. K2CO3 to yield 28.5 g. Et (-)-2-ethoxycarbonyl-1-pyrrolizinebutyrate (VII), b0.1 132.degree.; [.alpha.]13D -63.7.degree. (c 0.54). Treatment of 15 g. VII with NaOEt (as for VI) yielded 3 g. Et (-)-octahydro-8-oxo-7-indolizinecarboxylate (VIII), b0.05 99-102.degree.; [.alpha.]19D -25.1.degree. (c 2.7); the PhMe layer yielded 4.2 g. starting compd. VII, indicating the occurrence of racemization. VIII (3 g.) was decarboxylated by heating 25 hrs. on a water bath with 20 ml. 10% HCl to yield 1.3 g. hexahydro-8(5H)-indolizinone (IX), b5 65-7.degree.; [.alpha.]16D .+-.0.degree. (l = 1 cm.; neat) [oxime m. 117-18.degree. (iso-PrOH); picrate m. 147-8.degree. (EtOH)]. A soln. of 3.6 g. dl-IX and 8.5 g. Va in 40 ml. Me2CO was left 2 days at room temp. to give 8.3 g. of the corresponding Va salt monohydrate, m. 130-1.degree.; [.alpha.]17D 56.8.degree. (c 2.07, H2O); the amino ketone (b15 90-8.degree.) recovered from the salt was optically inactive. Alternatively, 5.6 g. dl-IX and 9.6 g. d-10-camphorsulfonic acid in 60 ml. Me2CO and 20 ml. abs. ether was kept overnight in the refrigerator to yield 5 g. (+)-hexahydro-8(5H)-indolizinone 10-camphorsulfonate monohydrate, m. 97-101.degree. (Me2CO); [.alpha.]15D 16.0.degree. (c 2, H2O); the amino ketone [.alpha.]13D 0.93.degree. (c 4.3) [oxime HCl salt m. 176.degree. (EtOH); [.alpha.]14D 7.9.degree. (c 1.7, H2O)]. Ethyl (+)-2-ethoxycarbonyl-1-**piperidinebutyrate** (X) (13 g.) (b17 100.degree.; [.alpha.]28D 13.3.degree. (c 3.12)] was obtained from 10.2 g. D-pipecolic acid Et ester in the same way as VII. Treatment of X with NaOEt (as for I) yielded 50% hexahydro-2H-quinolizin-1-(6H)-one (XI), b3-5 80-90.degree.; [.alpha.]30D .+-.0.degree. (c 10 [picrate m. 166-7.degree. (EtOH); semicarbazone, m. 214.degree. (EtOH); oxime HCl salt m. 214.degree. (EtOH-iso-Pr2O). X (4 g.) was subjected to the Dieckmann cyclization using NaOEt (from 0.35 g. Na) in the same way as VI to yield 0.85 g. Et (+)-octahydro-1-oxo-2-quinolizine-carboxylate, b0.15 109-15.degree.; [.alpha.]32D 38.6.degree. (c, 3.0). A soln. of 5.8 g. dl-XI and 12 g. Va in 30 ml. Me2CO was left overnight at room temp. to yield 4 g. (-)-hexahydro-2H-quinolizin-1(6H)-one 3-bromo-8-camphorsulfonate, m. 195-6.degree.; [.alpha.]20D 61.2.degree. (c 2, H2O), which yielded (-)-XI, b8 93-5.degree.; [.alpha.]10D -37.degree. (c 5.5); [.alpha.]22D -31.7.degree. (c 3.3, isooctane); Analogous treatment of the mother liquor afforded the enantiomeric (+)-XI, [.alpha.]20D 22.7.degree. (c 1.88) [oxime HCl salt; [.alpha.]20D 38.6.degree. (c 1, H2O)]. L-Phenylalanine was subjected to the Pictet-Spengler reaction by the method of Archer (CA 46: 2548i) to give 1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid hydrochloride, which on esterification (SOCl2-EtOH) afforded 60% Et (-)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (XII), b0.2 115-21.degree.; [.alpha.]20D -76.8.degree. (c 0.7) [HCl salt, m. 203-5.degree. (decompn.) (EtOH); [.alpha.]20D -85.7.degree. (c 1.2, H2O); picrate m. 198-9.degree. (EtOH)].

Ethyl (-)-3-ethoxycarbonyl-1,2,3,4-tetrahydro-2-isoquinolinebutyrate (XIII) [b2-3 180-90.degree.; [.alpha.]28D -7.4.degree. (c 5)] was prepd. from the ester XII in 50% yield according to the modified procedure described for VII. XIII (12.1 g.) and 0.91 g. NaH in 120 ml. abs. dioxane was gently refluxed 1 hr. under N to yield 5.5 g. Et (-)-1,3,4,6,11,11a-hexahydro-1-oxo-2H-benzo(b)quinolizine-2-carboxylate (XIV), m. 79-9.5.degree.; [.alpha.]28D -13.3.degree. (c 1.5). Decarboxylation of 1.5 g. XIV by heating 1.5 hrs. in 15 ml. 10% HCl yielded 0.65 g.

3,4,11,11a-tetrahydro-2H-benzo[b]quinolizin-1(6H)-one (XIVa), m. 96-8.degree.; [.alpha.]25D .+-.0.degree. (c 1.5). The rate consts. and half-times for recemization of III, V, IX, and XI were detd. under various conditions, at 20.degree., and in aq. EtOH. III was found to be racemized very rapidly, while in HCl, no racemization was observed.

L3 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2000 ACS
AN 1967:454417 CAPLUS
DN 67:54417
TI Optically active **amino acids**. XIII. **Racemization** of N-benzoylanilides of optically active **proline** and pipecolic acid
AU Kunieda, Takehisa; Koga, Kenji; Yamada, Shunichi
CS Univ. Tokyo, Tokyo, Japan
SO Chem. Pharm. Bull. (1967), 15(3), 350-1
CODEN: CPBTAL
DT Journal
LA English
AB CA 67: 22124d. Effect of ring size on rate of **racemization** of monocyclic .alpha.-**amino acid** derivs. such as (-)-1-benzoyl-2-pyrrolidinecarboxanilide (I) and (+)-1-benzoyl-2-**piperidinecarboxanilide** (II) is studied. N,N'-Dicyclohexylcarbodiimide (2 g.) was added to a soln. of 2.1 g. N-benzoyl-L-**proline** (III) and 0.93 g. PhNH2 in 45 ml. CH2Cl2, stirred at room temp. 3.5 hrs., clarified by filtration, washed with aq. NaHCO3 soln., and concd. to give 1.7 g. I, m. 185-6.degree., [.alpha.]14D -115.6.degree. (c 1.6, EtOH). A mixt. of 6.57 g. III and 3.03 g. Et3N in 120 ml. abs. PhMe at -7 to -5.degree. was treated with 3.26 g. ClCO2Et, kept at -5.degree. for 25 min., treated with 2.8 g. PhNH2, allowed to stand overnight, clarified by filtration, washed with dil. HCl and aq. NaHCO3 soln., and concd. to give 5.5 g. I. II, m. 167-9.degree., [.alpha.]18D 55.8.degree. (c 1.04, EtOH), was similarly prepd. Their rate of **racemization** was measured polarimetrically in Me2SO soln. at 40 .+-. 0.5.degree., using 3 moles of NaOEt as a base to show that I **racemized** 6 times faster than II.

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=> s methyl(l)pheni?

        515607 METHYL
          2391 PHENI?
L5         130 METHYL(L)PHENI?

=> s l5 and racemiz?

          6537 RACEMIZ?
L6           0 L5 AND RACEMIZ?

=> s l5 and threo?

         41378 THREO?
L7           6 L5 AND THREO?

=> d bib abs 1-6


L7   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2000 ACS
AN   2000:113124  CAPLUS
DN   132:151683
TI   Enantioselective synthesis of methyl phenidate
IN   Winklter, Jeffrey David; Axten, Jeffrey M.; Krim, Lori
PA   The Trustees of the University of Pennsylvania, USA
SO   U.S., 11 pp.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   US 6025502          A    20000215       US 1999-273144   19990319
OS   MARPAT 132:151683
AB   The D-threo isomer of Me phenidate is prepd.
     selectively by reaction of N-BOC piperidine (I) with PhC(:N2)COOMe (II)
in
     the presence of dirhodium tetrakis[methyl 2-oxopyrrolidine-5(R)-
     carboxylate] as catalyst.  Related compds. can be prepd. by using, e.g.,
     N-BOC pyrrolidine, instead of I and, e.g., Et phenyldiazoacetate, Me
     1-naphthyldiazoacetate, or Et 1-naphthyldiazoacetate instead of II.
RE.CNT  25
RE
(4) Anon; WO 9727176 1997 CAPLUS
(5) Anon; WO 9727176 1997 CAPLUS
(6) Anon; WO 9728124 1997 CAPLUS
(7) Anon; WO 9735836 1997 CAPLUS
(8) Anon; WO 9825902 1998 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7   ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2000 ACS
AN   1999:392473  CAPLUS
DN   131:157698
TI   Enantioselective Synthesis of D-threo-Methylphenidate
AU   Axten, Jeffrey M.; Ivy, Robert; Krim, Lori; Winkler, Jeffrey D.
CS   Department of Chemistry, The University of Pennsylvania, Philadelphia,
PA,
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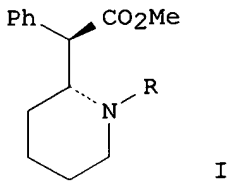
19104, USA
SO J. Am. Chem. Soc. (1999), 121(27), 6511-6512
CODEN: JACSAT; ISSN: 0002-7863
PB American Chemical Society
DT Journal
LA English
OS CASREACT 131:157698
GI



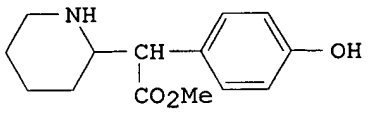
I

AB The hydrochloride of Me D-**threo**-phenidate I (Ritalin) (R = H) was prepd. enantioselectively in two steps from N-Boc piperidine and Me phenyldiazoacetate by an enantioselective C-H insertion reaction catalyzed by the dirhodium catalyst Rh2(5R-MEPY)4 to give the phenidate I (R = Boc) in 64% yield. Treatment of I (R = Boc) with methanolic HCl and two recrystns. from 1:1 ethanol:diethyl ether gave I as its hydrochloride in 26% yield (68% yield before recrystn.).
RE.CNT 32
RE
(2) Axten, J; J Org Chem 1998, V63, P9628 CAPLUS
(3) Calter, M; Curr Org Chem 1997, V1, P37 CAPLUS
(4) Dakin, L; Tetrahedron Lett 1998, V39, P8947 CAPLUS
(5) Davies, H; J Am Chem Soc 1997, V119, P9075 CAPLUS
(6) Dieter, R; J Org Chem 1997, V62, P7726 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 1998:482482 CAPLUS
DN 129:202841
TI Enzymic resolution of (.+-.)-**threo**-methylphenidate
AU Prashad, Mahavir; Har, Denis; Repic, Oljan; Blacklock, Thomas J.; Giannousis, Peter
CS Chemical and Analytical Development, Process Research and Development, Novartis Pharmaceuticals Corporation, East Hanover, NJ, 07936, USA
SO Tetrahedron: Asymmetry (1998), 9(12), 2133-2136
CODEN: TASYE3; ISSN: 0957-4166
PB Elsevier Science Ltd.
DT Journal
LA English
OS CASREACT 129:202841
AB The resoln. of (.+-.)-**threo**-methylphenidate by enzymic hydrolysis with .alpha.-chymotrypsin or subtilisin carlsberg to afford (2S,2'S)-(-)-**threo** and (2R,2'R)-(+)-**threo** -methylphenidate hydrochlorides in high enantiomeric purities is described.

L7 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 1981:525869 CAPLUS
DN 95:125869
TI Synthesis and pharmacology of hydroxylated metabolites of **methyl phenidate**
AU Patrick, Kennerly S.; Kilts, Clinton D.; Breese, George R.
CS Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27514, USA
SO J. Med. Chem. (1981), 24(10), 1237-40

CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
GI



I

AB Me **threo**-dl- (I) [78708-74-4] and erythro-dl-p-hydroxymethylphenidate-HCl (II) [78708-67-5] and their resp. deesterified products III [78708-75-5] and IV [78708-76-6] were synthesized and tested for dopaminergic activity in rats. The locomotor response to I was greater than that to II, ritalin (V) [298-59-9], or erythro-dl-methylphenidate-HCl [23644-60-2], suggesting that I may play a role in the pharmacol. of V in the hyperkinetic syndrome in children. **threo**-dl-Ritalinic acid-HBr [78708-68-6], erythro-dl-ritalinic acid-HBr [78779-59-6], III, and IV produced small increases in locomotor activity relative to their Me esters and the responses were not appreciably affected by stereochem. or para-hydroxylation.

L7 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 1975:118724 CAPLUS
DN 82:118724
TI Metabolism and disposition of **methyl phenidate**-14C: Studies in man and animals
AU Faraj, B. A.; Israili, Z. H.; Perel, J. M.; Jenkins, M. L.; Holtzman, S. G.; Cucinell, S. A.; Dayton, P. G.
CS Dep. Med., Emory Univ., Atlanta, Ga., USA
SO J. Pharmacol. Exp. Ther. (1974), 191(3), 535-47
CODEN: JPETAB
DT Journal
LA English
GI For diagram(s), see printed CA Issue.
AB 14C-labeled **threo**-dl-methylphenidate-HCl (**threo**-dl-I-HCl) [23655-65-4] was extensively metab. in man, dog, rat and mouse but with pronounced species differences. In human subjects, blood plasma levels of I were also much higher after i.v. than after oral administration. After oral administration, 50 and 90% of the 14C was excreted in urine in 8 and 48 hrs, resp. This suggests esentially complete absorption of I. The main urinary metabolite was the deesterified product, **threo**-dl-ritalinic acid [54631-24-2], accounting for 80% of the dose. Upon i.v. administration of I to dogs, 50-60% of the radioactivity was excreted in 7 hr urine. The major metabolites in dog urine were ritalinic acid and **threo**-dl-2-phenyl-2-(2'-piperidyl-6'-one)acetic acid [54593-31-6]. In rats, both after i.p. and oral administration of I, 50-60% of the 14C was eliminated in urine and 30-40% in feces within 48 hrs. Significant biliary excretion of 14C (25-30% in 12 hrs) was found bile-cannulated rats. The major metabolites in rat urine besides ritalinic acid were **threo**-dl-2-(p-hydroxyphenyl)-2-(2'-piperidyl)acetic acid [54593-32-7], its methyl ester [54593-35-0] and its glucuronide conjugate [54642-79-4]. The locomotor activity of I, certain metabolites and N-acetyl-**threo**-dl-methylphenidate [54593-33-8] was studied in mice.

L7 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2000 ACS
AN 1969:96027 CAPLUS
DN 70:96027